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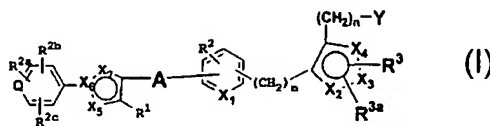
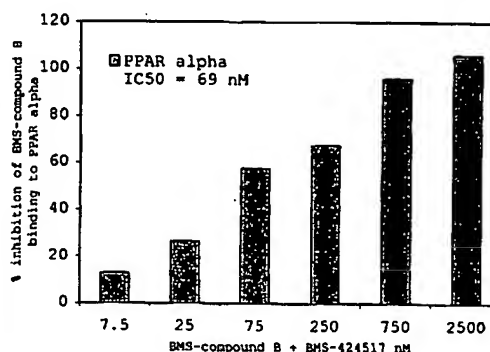
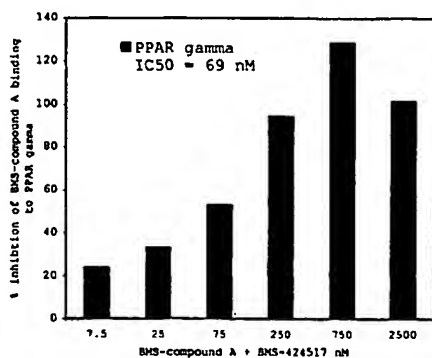
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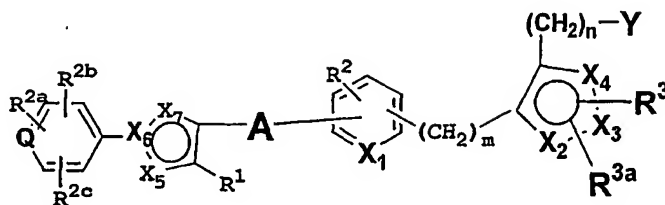
(54) Title: SUBSTITUTED AZOLE ACID DERIVATIVES USEFUL AS ANTIDIABETIC AND ANTI-OBESITY AGENTS AND METHOD



(57) Abstract: Compounds are provided which have the structure: (formula I); wherein Q is C or N; R^{2a}, R^{2b}, R^{2c}, X₁ to X₅, R¹, R², R³, R^{3a}, R⁴, A, Y, m, and n are as defined herein, which compounds are useful as antidiabetic, hypolipidemic, and antiobesity agents. The present invention further provides a method for treating obesity and dyslipidemia in mammals including humans through simultaneous inhibition of peroxisome proliferator activated receptor-γ (PPARγ) and stimulation of peroxisome proliferator activated receptor-α (PPARα).

What is Claimed is:

1. A compound which has the structure



5

wherein m is 0, 1 or 2; n = 0, 1 or 2;

Q is C or N

- A is $(\text{CH}_2)_x$ where x is 1 to 5; or A is $(\text{CH}_2)_{x^1}$,
 10 where x^1 is 2 to 5, with an alkenyl bond or an alkynyl
 bond embedded in the chain; or A is $-(\text{CH}_2)_{x^2}-\text{O}-(\text{CH}_2)_{x^3}-$
 where x^2 is 0 to 5 and x^3 is 0 to 5, provided that at
 least one of x^2 and x^3 is other than 0,

X_1 is CH or N

- 15 X_2 is C, N, O or S;

X_3 is C, N, O or S;

X_4 is C, N, O or S, provided that at least one of
 X_2 , X_3 and X_4 is N;

X_5 is C, N, O or S;

- 20 X_6 is C or N;

X_7 is C, N, O or S, provided that at least one of
 X_5 , X_6 or X_7 is N; and where in each of X_1 through X_7 , as
 defined above, C may include CH;

R^1 is H or alkyl;

- 25 R^2 is H, alkyl, alkoxy, halogen, amino or
 substituted amino;

R^{2a} , R^{2b} and R^{2c} are the same or different and are
 selected from H, alkyl, alkoxy, halogen, amino or
 substituted amino;

- 30 R^3 and R^{3a} are the same or different and are
 independently selected from H, alkyl, arylalkyl,
 aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl,
 alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl,

- heteroaryl, alkyl(halo)aryloxy carbonyl,
 alkyloxy(halo)aryloxy carbonyl cycloalkylaryloxy carbonyl,
 cycloalkyloxyaryloxy carbonyl, cycloheteroalkyl,
 heteroarylcarbonyl, heteroaryl-heteroarylalkyl,
 5 alkylcarbonylamino, arylcarbonylamino,
 heteroarylcarbonylamino, alkoxycarbonylamino,
 aryloxy carbonylamino, heteroaryloxy carbonylamino,
 heteroaryl-heteroarylcarbonyl, alkylsulfonyl,
 alkenylsulfonyl, heteroaryloxy carbonyl,
 10 cycloheteroalkyloxy carbonyl, heteroarylalkyl,
 aminocarbonyl, substituted aminocarbonyl,
 alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl,
 cycloheteroalkylheteroarylalkyl, hydroxyalkyl, alkoxy,
 alkoxyaryloxy carbonyl, arylalkyloxy carbonyl,
 15 alkylaryloxy carbonyl, arylheteroarylalkyl,
 arylalkylarylalkyl, aryloxyarylalkyl, alkynyloxy carbonyl,
 haloalkoxyaryloxy carbonyl, alkoxycarbonylaryloxy carbonyl,
 aryloxyaryloxy carbonyl, arylsulfinylarylcarbonyl,
 arylthioarylcarbonyl, alkoxycarbonylaryloxy carbonyl,
 20 arylalkenyloxy carbonyl, heteroaryloxyarylalkyl,
 aryloxyarylcarbonyl, aryloxyarylalkyloxy carbonyl,
 arylalkenyloxy carbonyl, arylalkylcarbonyl,
 aryloxyalkyloxy carbonyl arylalkylsulfonyl,
 arylthiocarbonyl, arylalkenylsulfonyl,
 25 heteroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl,
 heteroarylalkoxy carbonyl, arylheteroarylalkyl,
 alkoxyarylcarbonyl, aryloxyheteroarylalkyl,
 heteroarylalkyloxyarylalkyl, arylarylalkyl,
 arylalkenylarylalkyl, arylalkoxyarylalkyl,
 30 arylcarbonylarylalkyl, alkylaryloxyarylalkyl,
 arylalkoxy carbonylheteroarylalkyl, heteroarylarylalkyl,
 arylcarbonylheteroarylalkyl, heteroaryloxyarylalkyl,
 arylalkenylheteroarylalkyl, arylaminoarylalkyl or
 aminocarbonylarylalkyl;
 35 Y is CO₂R⁴ (where R⁴ is H or alkyl, or a prodrug
 ester) or Y is a C-linked 1-tetrazole, a phosphinic acid
 of the structure P(O)(OR^{4a})R⁵, (where R^{4a} is H or a prodrug

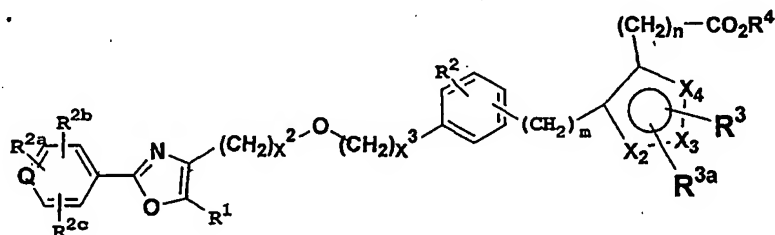
ester, R^5 is alkyl or aryl) or a phosphonic acid of the structure $P(O)(OR^{4a})_2$;

$(CH_2)_x$, $(CH_2)_x^1$, $(CH_2)_x^2$, $(CH_2)_x^3$, $(CH_2)_m$, and $(CH_2)_n$ may be optionally substituted with 1, 2 or 3 substituents;

5 including all stereoisomers thereof, a prodrug ester thereof, and a pharmaceutically acceptable salt thereof.

2. A compound having the structure

10



wherein m is 0, 1 or 2; $n = 0, 1$ or 2;

Q is C or N

15 x^2 is 0 to 5 and x^3 is 0 to 5, provided that at least one of x^2 and x^3 is other than 0,

X_2 is C, N, O or S;

X_3 is C, N, O or S;

X_4 is C, N, O or S, provided that at least one of

20 X_2 , X_3 and X_4 is N;

and where in each of X_2 through X_4 , as defined above, C may include CH;

R^1 is H or alkyl;

25 R^2 is H, alkyl, alkoxy, halogen, amino or substituted amino;

R^{2a} , R^{2b} and R^{2c} are the same or different and are selected from H, alkyl, alkoxy, halogen, amino or substituted amino;

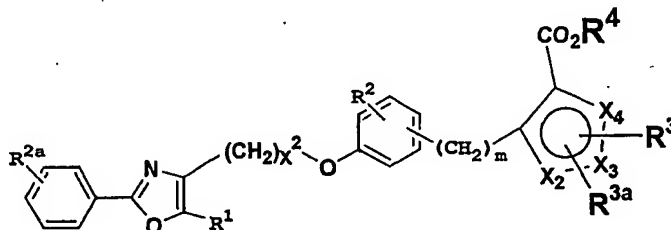
30 R^3 and R^{3a} are the same or different and are independently selected from H, alkyl, arylalkyl, aryloxy carbonyl, alkyloxy carbonyl, alkynyloxy carbonyl, alkenyloxy carbonyl, aryl carbonyl, alkyl carbonyl, aryl, heteroaryl, alkyl(halo)aryloxy carbonyl,

alkyloxy(halo)aryloxycarbonyl cycloalkylaryloxycarbonyl,
 cycloalkyloxyaryloxycarbonyl, cycloheteroalkyl,
 heteroarylcarbonyl, heteroaryl-heteroarylalkyl,
 alkylcarbonylamino, arylcarbonylamino,
 5 heteroarylcarbonylamino, alkoxycarbonylamino,
 aryloxycarbonylamino, heteroaryloxycarbonylamino,
 heteroaryl-heteroarylcarbonyl, alkylsulfonyl,
 alkenylsulfonyl, heteroaryloxycarbonyl,
 cycloheteroalkyloxycarbonyl, heteroarylalkyl,
 10 aminocarbonyl, substituted aminocarbonyl,
 alkylaminocarbonyl, arylaminocarbonyl, heteroarylalkenyl,
 cycloheteroalkylheteroarylalkyl, hydroxyalkyl, alkoxy,
 alkoxyaryloxycarbonyl, arylalkyloxycarbonyl,
 alkylaryloxycarbonyl, arylheteroarylalkyl,
 15 arylalkylarylalkyl, aryloxyarylalkyl, alkynyloxycarbonyl,
 haloalkoxyaryloxycarbonyl, alkoxycarbonylaryloxycarbonyl,
 aryloxyaryloxycarbonyl, arylsulfinylarylcarbonyl,
 arylthioarylcarbonyl, alkoxycarbonylaryloxycarbonyl,
 arylalkenyloxycarbonyl, heteroaryloxyarylalkyl,
 20 aryloxyarylcarbonyl, aryloxyarylalkyloxycarbonyl,
 arylalkenyloxycarbonyl, arylalkylcarbonyl,
 aryloxyalkyloxycarbonyl arylalkylsulfonyl,
 arylthiocarbonyl, arylalkenylsulfonyl,
 heteroarylsulfonyl, arylsulfonyl, alkoxyarylalkyl,
 25 heteroarylalkoxycarbonyl, arylheteroarylalkyl,
 alkoxyarylcarbonyl, aryloxyheteroarylalkyl,
 heteroarylalkyloxyarylalkyl, arylarylalkyl,
 arylalkenylarylalkyl, arylalkoxyarylalkyl,
 arylcarbonylarylalkyl, alkylaryloxyarylalkyl,
 30 arylalkoxycarbonylheteroarylalkyl, heteroarylarylalkyl,
 arylcarbonylheteroarylalkyl, heteroaryloxyarylalkyl,
 arylalkenylheteroarylalkyl, arylaminoarylalkyl or
 aminocarbonylarylalkyl;

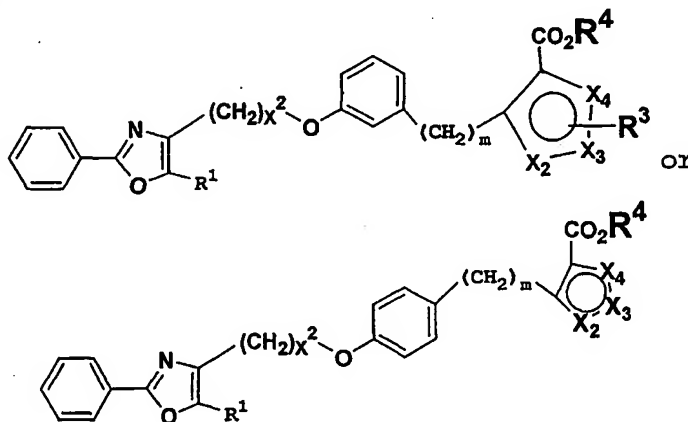
(CH₂)_x², (CH₂)_x³, (CH₂)_m, and (CH₂)_n may be optionally
 35 substituted with 1, 2 or 3 substituents;

including all stereoisomers thereof, a prodrug ester thereof, and a pharmaceutically acceptable salt thereof.

- 5 3. The compound as defined in Claim 1 having the structure



- 10 4. The compound as defined in Claim 1 having structure

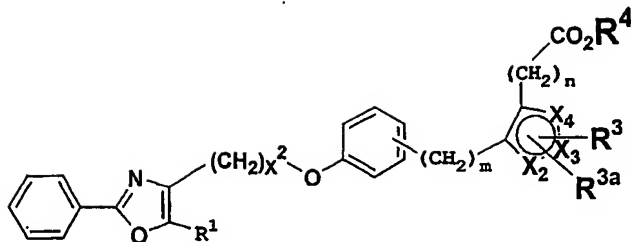


- 15 5. The compound as defined in Claim 1 wherein $(CH_2)_x$, $(CH_2)_x^1$, $(CH_2)_x^2$, $(CH_2)_x^3$ are alkylene, alkenylene, allenyl, or alkynylene.

- 20 6. The compound as defined in Claim 1 wherein X_1 is CH.

7. The compound as defined in Claim 1 wherein X is N.

- 25 8. The compound as defined in Claim 1 having the structure

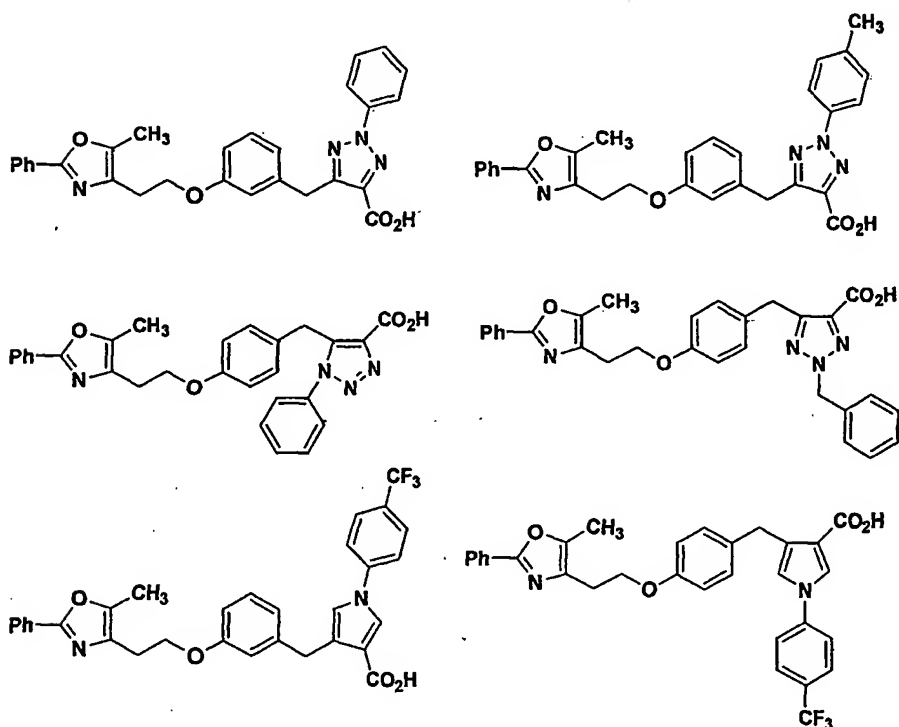


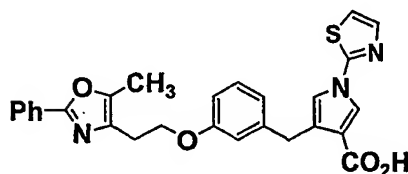
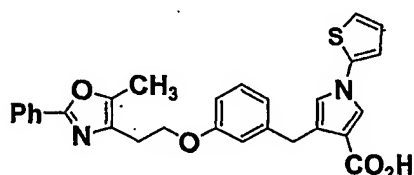
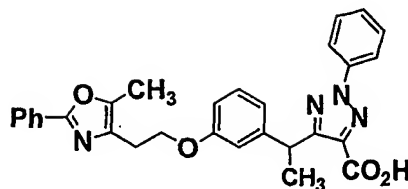
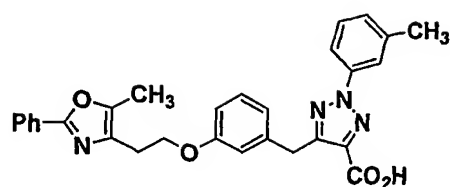
wherein R^1 is alkyl, x^2 is 1, 2 or 3, m is 0 or 1, or
 $(CH_2)_m$ is $CHOH$ or CH -alkyl, n is 1, $(CH_2)_n$ is a bond or
 5 CH_2 , X_2 , X_3 , and X_4 represent a total of 1, 2 or 3
 nitrogens, R^3 is aryl, arylalkyl or heteroaryl and R^{3a} is
 H or alkyl.

9. The compound as defined in Claim 8 wherein R^1 is
 10 CH_3 , and R^3 is phenyl or phenyl substituted with alkyl,
 polyhaloalkyl, halo or alkoxy.

10. The compound as defined in Claim 1 having the
 structure

15





11. A pharmaceutical composition comprising a
compound as defined in Claim 1 and a pharmaceutically
5 acceptable carrier therefor.

12. A method for lowering blood glucose levels,
or for treating diabetes which comprises administering to
a patient in need of treatment a therapeutically
10 effective amount of a compound as defined in Claim 1.

13. A method for treating a premalignant disease,
an early malignant disease, a malignant disease, or a
dysplastic disease, which comprises administering to a
15 patient in need of treatment a therapeutically effective
amount of a compound as defined in Claim 1.

14. A pharmaceutical combination comprising a
compound as defined in Claim 1 and a lipid-lowering
20 agent, a lipid modulating agent, an antidiabetic agent,
an anti-obesity agent, an antihypertensive agent, a
platelet aggregation inhibitor, and/or an
antiosteoporosis agent, wherein the antidiabetic agent is
1, 2, 3 or more of a biguanide, a sulfonyl urea, a
25 glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual
agonist, an SGLT2 inhibitor, a DP4 inhibitor, an α P2
inhibitor, an insulin sensitizer, a glucagon-like
peptide-1 (GLP-1), insulin and/or a meglitinide, wherein

the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor agonist, an α 2 inhibitor and/or an anorectic agent, wherein the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor, ~~wherein the anti-hypertensive agent is an ACE inhibitor, angiotensin II receptor antagonist, NEP/ACE inhibitor, calcium channel blocker and/or β -adrenergic blocker.~~

15. The combination as defined in ~~Claim 12~~ wherein the ~~antidiabetic agent is 1, 2, 3 or more of~~ metformin, glyburide, glimepiride, glipyrilide, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, ~~JMT-5501~~, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-20 HO39242, ~~GW-4109544~~, ~~KRP-297~~, AC2993, LY315902, P32/98 and/or NVP-DPP-728A, wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol, wherein the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, itavastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, cholestagel, niacin and/or LY295427, ~~wherein the~~ ~~anti-hypertensive agent is an ACE inhibitor~~ which is captopril, fosinopril, enalapril, lisinopril, quinapril, benazepril, fentiapril, ramipril or moexipril; an NEP/ACE inhibitor which is omapatrilat, [S[(R*,R*)]-hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (gemopatrilat) or CGS 30440; ~~an angiotensin II receptor antagonist which is~~ ~~irbesartan, losartan or valsartan;~~

amlodipine besylate, prazosin HCl, verapamil, nifedipine, nadolol, propranolol, carvedilol, or clonidine HCl, wherein the platelet aggregation inhibitor is aspirin, clopidogrel, ticlopidine, dipyridamole or
5 ifetroban.

16. A method for treating insulin resistance, hyperglycemia, hyperinsulinemia, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity,
10 Syndrome X, dysmetabolic syndrome, inflammation, diabetic complications, impaired glucose homeostasis, impaired glucose tolerance, hypertriglyceridemia or atherosclerosis which comprises administering to a mammalian species in need of treatment a therapeutically
15 effective amount of a pharmaceutical combination as defined in Claim 14.

17. The method as defined in Claim 13 wherein the disease is a liposarcoma or an epithelial tumor.
20

18. The method as defined in Claim 17 wherein the epithelial tumor is a tumor of the breast, prostate, colon, ovaries, stomach or lung.

25 19. A method for treating irritable bowel syndrome, Crohn's disease, gastric ulceritis or osteoporosis, or psoriasis, or for treating obesity, insulin resistance, dyslipidemia, cardiovascular diseases and liver abnormalities, which comprises administering to a
30 mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

20. ~~A method for treating obesity and cardiovascular disease~~ through altering the expression of a gene selected from the following: HMGic, glycerol-PO₄ dehydrogenase, fatty acid transport protein, G-protein
- 5 coupled receptor 26, adipophilin, keratinocyte, fatty acid binding protein, ~~angiotensinogen~~, PAI-1, and renin, ~~through administration of a dual PPARgamma antagonist/PPARalpha agonist.~~